Obesity and Risk of Renal Cell Cancer

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Abstract

In a population-based case-control study including 449 directly interviewed cases and 707 controls, we assessed the risk of renal cell cancer associated with height, weight, body mass index (BMI), and frequency of weight changes. Odds ratios and 95% confidence intervals were estimated by using logistic regression models. Among women, risk increased with increasing usual BMI (*P* for trend < 0.001). A nearly 4-fold risk was found among the 10% of women with the highest usual BMI (odds ratio = 3.8; confidence interval = 1.7–8.4). Among men, no clear trend was observed with usual weight or BMI, although the highest risk (30–50%) generally was seen among those in the upper deciles of weight or BMI. There was no clear indication that excess BMI early or late in life disproportionately affected risk. Risk also was not related to patterns of weight fluctuations or use of diet pills. Our study supports previous observations linking renal cell cancer risk to increased BMI among women and suggests a weaker association in men. Given the increasing prevalence of obesity and the rising incidence of renal cell cancer in the United States, additional studies are needed to disentangle the effects of BMI from various correlates and to identify the mechanisms by which obesity affects risk.

Introduction

Along with cigarette smoking and a history of hypertension and/or its treatment, obesity has been linked consistently to renal cell cancer, especially among women (1, 2). In addition, recent findings from Sweden suggest that weight cycling may be a risk factor independent of obesity (3). Because cigarette smoking may influence weight (4, 5), which in turn may affect the development and course of hypertension (6, 7), it is important to investigate these risk factors in relation to one another. In a large population-based case-control study in Minnesota, we examined the risk of renal cell cancer associated with obesity and weight fluctuations, and the effect modifications with cigarette smoking and a history of hypertension.

Subjects and Methods

Methods for this study have been presented in detail elsewhere (8). Briefly, residents of Minnesota between the ages of 20 and 79 years who were newly diagnosed with a histologically confirmed renal cell cancer (International Classification of Diseases-9 code 189.: Ref. 9) between July 1, 1988 and December 31, 1990, were identified through the state cancer surveillance system (10). Of the 796 eligible cases, interviews were obtained for 690 (87%), including 241 interviews with NOK[3] for patients who died or were too ill to be interviewed.

The controls were randomly selected from residents in Minnesota by using a random digit dialing method (11) for those under age 65 years and Medicare files maintained by the Health Care Financing Administration for those ages 65 years or older (12); they were frequency-matched to cases by sex and age in 5-year groups. Overall interview response rate was 87% for Health Care Financing Administration controls and 84% for random digit dialing controls, based on a 93% response rate at the household-screening phase and a 90% response rate at the interview phase. A total of 707 controls were interviewed.

In-person interviews were conducted in the homes of study subjects by trained interviewers by using a structured questionnaire to elicit information on demographic characteristics, height, history of weight and selected medical conditions, use of analgesic and antihypertensive drugs, tobacco and alcohol intake, and occupational history. BMI was computed for men (weight in kg/height in meter^2) and women (weight in kg/height in meter$^{1.5}$) (13), using the usual adult weight and weight in each decade of life (20s, 30s, 40s, and 50s). The variables were grouped into quintiles separately for men and women based on distributions among controls, with the last quintile further divided into the 81–90 percentile and 91–100 percentile (upper decile) for selected analyses. The cut points for quintiles of selected variables are presented in the Appendix.

Data were analyzed using stratified methods and logistic regression models to evaluate multivariate relationships and to adjust for confounding factors. Summary ORs and corresponding 95% CIs were computed to measure risk of renal cell cancer associated with BMI and other related variables (14). Risk estimates were based only on information from directly interviewed cases and controls, whereas information from NOK cases was examined separately to evaluate the consistency of associations in the study.

Results

Directly interviewed cases and controls were similar in distribution by sex (63% male cases and 67% male controls), age

Received 4/19/95; revised 7/6/95; accepted 7/7/95.
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[3] The abbreviations used are: NOK, next of kin; BMI, body mass index; OR, odds ratio; CI, confidence interval.

Table 1 ORs and 95% CIs for renal cell cancer in relation to height, weight, and BMI

Quintiles of measurement	Men				Women			
	Control	Case	OR	95% CI	Control	Case	OR	95% CI
Height[a]								
Q1	93	51	1.0		32	27	1.0	
Q2	101	65	1.1	0.7–1.8	57	46	0.8	0.4–1.7
Q3	89	49	0.9	0.6–1.6	55	31	0.6	0.3–1.2
Q4	72	35	0.8	0.5–1.4	22	13	0.6	0.2–1.5
81–90% Q5	56	41	1.2	0.7–2.2	27	21	0.8	0.3–1.8
91–100% Q5	50	33	0.9	0.5–1.8	30	25	0.7	0.3–1.7
Usual weight[b]								
Q1	94	52	1.0		44	18	1.0	
Q2	86	33	0.7	0.4–1.2	53	29	1.6	0.8–3.3
Q3	116	76	1.2	0.7–2.0	34	18	1.4	0.6–3.1
Q4	69	34	0.9	0.5–1.6	51	42	2.1	1.0–4.3
81–90% Q5	47	35	1.2	0.7–2.3	20	23	2.9	1.2–6.8
91–100% Q5	48	44	1.5	0.8–2.8	21	33	3.4	1.5–7.8
Usual BMI[c]								
Q1	92	54	1.0		45	17	1.0	
Q2	96	44	0.8	0.5–1.2	45	22	1.4	0.6–2.9
Q3	93	47	0.8	0.5–1.4	44	24	1.4	0.6–3.0
Q4	87	58	1.1	0.7–1.7	45	47	2.6	1.3–5.2
81–90% Q5	46	33	1.1	0.6–2.0	22	17	1.9	0.8–4.7
91–100% Q5	46	38	1.3	0.7–2.3	22	36	3.8	1.7–8.4

[a] Adjusted for age, smoking, a history of hypertension/hypertensive drug use, and usual weight.
[b] Adjusted for age, smoking, a history of hypertension/hypertensive drug use, and height.
[c] Adjusted for age, smoking, and a history of hypertension/hypertensive drug use.

(mean age was 61.4 for cases and 62 for controls) and educational level (25% each of cases and controls did not graduate from high school, and 32% of cases and 34% of controls had some college). On the other hand, cases were more likely to be current smokers (26% cases *versus* 22% controls) and to have a history of hypertension or to use antihypertensive drugs (53% cases *versus* 40% controls).

Risk of renal cell cancer was not associated with height in either sex. Among men, risks were elevated 30–50% among those in the upper deciles of usual weight and usual BMI (Table 1). Among women, risks tended to rise with increasing usual weight (P for trend = 0.001) or usual BMI ($P < 0.001$). A greater than 3-fold risk was observed among women in the upper deciles of usual weight (OR = 3.4; CI = 1.5–7.8) and usual BMI (OR = 3.8; CI = 1.7–8.4). There were no clear secular trends over decades of life for risks associated with BMI in either sex (data not shown).

The association between usual BMI and renal cell cancer was not modified by smoking status or protein intake, risk factors observed previously in our study (Table 2). However, relative to those in the lowest quintile of BMI without a history of hypertension/antihypertensive drug use, risks increased additionally among men (OR = 2.0; CI = 1.1–3.6) and women (OR = 5.3; CI = 2.1–13.2) in the highest quintile of BMI and with a history of hypertension or use of antihypertensive drugs. Risk also increased further (OR = 6.1; CI = 2.1–17.8) among women in the highest quintile of BMI who had had three or more births.

Risk of renal cell cancer was examined according to patterns of weight fluctuations (Table 3). Among men, risk was not affected by percentage of greatest weight gain, age at greatest weight gain, and number of times weight changed by 20 or more pounds. Among women, risk was not associated with number of times weight changed by 10 or more pounds. Relative to women with little or no weight gain, elevated risks were found with higher percentage weight gains, although the trend was not smooth. Furthermore, the effect of usual BMI was not modified by a history of weight change for either sex (data not shown). Regular use of diet pills in the past was associated with nonsignificant excess risks among men (OR = 1.7; CI = 0.7–4.1) and women (OR = 1.2; CI = 0.6–2.4; Table 3). The findings were similar whether diet pills were used for weight control or for other reasons.

The associations with BMI were not altered after additional adjustment for a history of renal diseases or parity among women. After adjustment for age, smoking, and a history of hypertension/antihypertensive drug use, no association was found between renal cell cancer and usual BMI among male NOK cases, whereas a 40% excess risk (OR = 1.4; CI = 0.6–3.5) was seen among female NOK cases in the highest quintile of usual BMI. Only three cases (one male and two female) were reported to have used diet pills by their NOK.

Discussion

With a few exceptions (15, 16), previous case-control studies have generally linked obesity to renal cell cancer among women (3, 17–27), whereas the association among men has been less clear (3, 26–28). In several cohort studies, increased risks have been shown among both women and men who had elevated weight or were classified as obese (29–31). The elevated risks we observed among women with increasing BMI are consistent with most studies. The slightly elevated risks seen among men in our study were limited to those with the highest BMI.

It is not clear why the effect of obesity on the risk of renal cell cancer is more pronounced among women than men. Accuracy in self-reported height and weight may vary by gender and age, with overreporting of height especially among elderly men (32, 33). The resulting underestimate of BMI among older

Table 2 ORs and 95% CIs for renal cell cancer in relation to usual BMI and other risk factors

	Quintiles of usual BMI									
	Q1		Q2		Q3		Q4		Q5	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Smoking status[a]										
Men										
Nonsmoker	1.0		0.6	0.2–1.8	0.4	0.1–1.3	0.6	0.2–1.7	0.7	0.2–2.0
Smoker	0.9	0.4–2.1	0.8	0.3–1.7	0.9	0.4–2.0	1.2	0.5–2.6	1.3	0.6–2.8
Women										
Nonsmoker	1.0		1.2	0.4–3.8	1.7	0.5–5.0	2.5	0.9–7.0	3.3	1.2–8.9
Smoker	1.5	0.5–4.6	2.2	0.7–7.0	1.7	0.5–5.3	3.9	1.3–11.4	3.4	1.1–10.7
Hypertension/drug use[b,c]										
Men										
No	1.0		0.8	0.5–1.5	0.8	0.4–1.5	1.2	0.6–2.1	1.0	0.5–1.8
Yes	1.4	0.6–3.0	0.9	0.4–1.8	1.2	0.6–2.3	1.3	0.7–2.5	2.0	1.1–3.6
Women										
No	1.0		1.0	0.3–2.8	1.1	0.4–3.4	1.7	0.6–4.8	2.2	0.8–6.3
Yes	1.4	0.4–4.3	2.7	0.9–7.8	2.4	0.8–6.7	5.0	1.9–12.9	5.3	2.1–13.2
Protein intake[d]										
Men										
Low	1.0		0.5	0.2–1.1	0.9	0.4–1.8	0.9	0.4–2.0	1.3	0.6–2.8
High	1.5	0.7–2.9	1.5	0.8–3.1	1.2	0.6–2.3	1.6	0.8–3.1	1.7	0.9–3.2
Women										
Low	1.0		1.1	0.4–3.7	1.5	0.5–4.8	1.6	0.6–4.7	3.5	1.2–10.0
High	1.5	0.5–4.6	1.9	0.7–5.6	1.7	0.6–4.7	4.6	1.7–12.1	3.3	1.3–8.5
No. of births[d]										
Women										
0–2	1.0		1.3	0.4–4.6	1.6	0.4–6.0	3.4	1.1–11.1	3.0	1.0–9.1
3+	2.2	0.7–7.3	3.0	1.0–9.4	2.5	0.8–7.3	4.3	1.5–12.3	6.1	2.1–17.8

[a] OR adjusted for age and a history of hypertension/hypertensive drug use.
[b] Included a history of hypertension and use of diuretics or other antihypertensive drugs.
[c] OR adjusted for age and smoking.
[d] OR adjusted for age, smoking, and a history of hypertension/hypertensive drug use.

obese men may weaken the association seen in men. In our data, the lack of association with usual BMI was similar for men under age 65 years and those ages 65 years or older, except for the slightly elevated risk among the younger men in the upper decile of usual BMI (OR = 1.7; CI = 0.8–3.6). This observation appears to support the possibility of underestimating BMI among older obese men, although it could also be due to chance.

Differential prevalence of other risk factors related to obesity seems to be an unlikely explanation (4–7) because the associations we observed with BMI were adjusted for other risk factors identified in our study such as smoking, dietary protein, and a history of hypertension/antihypertensive drug use (8, 34).

The mechanism by which obesity predisposes to renal cell cancer is unclear, although hormonal factors are thought to play a role (3, 26). Renal adenomas and carcinomas were induced in male and ovariectomized female hamsters given high doses of estrogens (35–37). Sex hormone receptors also have been demonstrated in normal and malignant renal tissue in hamsters and in humans (38, 39). Obesity increases the levels of endogenous estrogens (40), as well as growth factors that may contribute to the development of renal cell cancer (41).

An alternative explanation is that hypertension or metabolic complications of obesity may result in kidney damage that increases susceptibility to carcinogens or promoting agents (42–44). In our data, however, the association with obesity persisted after controlling for other risk factors, such as history of hypertension or kidney diseases (1) and intake of meat, fat, or protein (8, 22). Because hypertension has been reported to be more prevalent among middle-aged Americans with central body fat (45), future studies of renal cell cancer should collect information to evaluate the overall degree of adiposity and the location of fat depots.

Another correlate of obesity is physical activity, which is generally not considered a risk factor for renal cell cancer (20, 26, 27), although one study suggested an increased risk among sedentary men but not women (3). Although we found no clear association with physical activity, additional study of this issue seems warranted.

Lindblad *et al.* (3) reported that the risk of renal cell cancer among women is increased by the frequency of weight change, especially among those who had lost >5 kg for two or more times. The effect of weight fluctuations was independent of BMI and was not seen among men. On the other hand, Mellemgaard *et al.* (27) observed no association with weight cycling, consistent with our finding that risk was unaffected by the frequency of weight change or loss exceeding 10 lbs in women or 20 lbs in men.

Some studies have suggested that risk of renal cell cancer may be increased by use of amphetamines for weight loss (1, 3, 19, 27), but it has been difficult to separate the effects of amphetamine use from obesity or its consequences. In addition, there is some evidence that risk may be increased by diuretics (25), which are occasionally used to reduce weight. Although our study suggested a weak association with amphetamine use, the number of users was too small to reach any conclusion. Given the increasing

Table 3 ORs and 95% CIs for renal cell cancer in relation to characteristics of weight change

	Men				Women			
	Control	Case	OR[a]	95% CI	Control	Case	OR[a]	95% CI
% of greatest wt gain								
Q1	129	75	1.0		54	25	1.0	
Q2	56	34	1.0	0.6–1.7	35	25	1.4	0.7–2.9
Q3	91	53	0.9	0.6–1.5	45	46	1.9	1.0–3.7
Q4	92	53	0.8	0.5–1.3	44	18	0.7	0.3–1.5
81–90% Q5	46	28	1.0	0.6–1.7	22	26	1.9	0.9–4.2
91–100% Q5	46	30	0.9	0.5–1.6	22	22	1.3	0.5–2.9
Age at greatest wt gain								
<25	79	56	1.0		36	35	1.0	
25–34	99	67	1.1	0.7–1.7	57	42	0.8	0.4–1.6
35–44	59	31	0.8	0.5–1.4	37	34	1.2	0.6–2.5
≥45	91	41	0.7	0.4–1.2	37	30	1.0	0.5–2.1
No. of times wt changed[b]								
0	179	109	1.0		56	31	1.0	
1	156	89	0.9	0.6–1.2	55	35	0.8	0.4–1.7
2	81	39	0.7	0.4–1.1	51	35	0.9	0.5–1.7
3+	43	37	1.1	0.7–1.9	60	58	1.0	0.5–2.0
Use of diet pills[c]								
No	445	260	1.0		197	134	1.0	
Yes	10	12	1.7	0.7–4.1	22	25	1.2	0.6–2.4

[a] Adjusted for age, smoking, a history of hypertension/hypertensive drug use, and usual BMI.
[b] Weight gained or lost for >20 lbs for men and >10 lbs for women.
[c] Use for at least twice a week for 1 month or longer.

Appendix
Cut points for quintiles of height, weight, and BMI[a]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
					81–90%	91–100%
Height (m)						
Men	≤1.70	1.71–1.75	1.76–1.78	1.79–1.80	1.81–1.83	≥1.84
Women	≤1.55	1.56–1.60	1.61–1.63	1.64–1.65	1.66–1.68	≥1.69
Usual (kg)						
Men	≤70.3	70.7–76.7	77.1–83.5	83.9–88.0	88.4–93.0	≥95.2
Women	≤54.5	54.8–59.0	59.8–63.1	63.5–69.4	70.3–74.9	≥77.0
Usual BMI						
Men	≤23.12	23.17–24.41	24.68–25.83	25.84–27.60	27.80–29.65	≥29.75
Women	≤26.75	26.89–28.45	28.46–30.57	30.58–33.74	33.75–36.46	≥36.57

[a] BMI for men, weight in kg/height in meters^2; BMI for women, weight in kg/height in meter$^{1.5}$.

prevalence of obesity in the United States population (46), the difficulty in achieving sustainable weight reduction (47), and the increasing incidence of renal cell cancer in the United States (48), additional studies are needed to disentangle the effects of obesity from various correlates, such as diet, physical activity, somatotypes, weight cycling, and diet pills.

Several limitations should be considered in interpreting our results. In an earlier evaluation of selection bias in a case-control study of renal adenocarcinoma (49), female cases who participated in that study were slightly more obese than were nonparticipating female cases. No association between participation and obesity was found among female controls or male cases and controls. If this bias existed in our data, the ORs associated with BMI among women would be somewhat overestimated. In addition, 34.9% of the cases in our study died before they could be interviewed. If obesity were related to improved survival among cases (50), the ORs among directly interviewed cases also would be overestimated. Risk estimates based on information provided by NOK of deceased cases were different from those estimated for directly interviewed cases. It is not clear to what extent these discrepancies may be due to factors that affect survival after diagnosis or to less accurate information on variables such as height, weight, and use of amphetamines provided by NOK. Despite the potential limitations, our findings are consistent with most earlier studies, including cohort studies that are not likely to be affected by survival or selection bias.

In summary, our population-based case-control study supports previous observations linking renal cell cancer risk to increased BMI among women. In addition, a small excess risk was seen among men with the highest BMI. Contrary to some recent reports, however, we found no clear association with frequency of weight change or use of amphetamines. Additional studies are needed to elucidate the mechanisms by which obesity increases the risk of renal cell cancer.

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